

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

11 Publication number:

0 080 371
A1

12

EUROPEAN PATENT APPLICATION

21 Application number: 82306235.1

51 Int. Cl.³: C 07 C 65/40, C 07 D 257/04

22 Date of filing: 23.11.82

30 Priority: 25.11.81 JP 189812/81
22.10.82 JP 186361/82

71 Applicant: Takeda Chemical Industries, Ltd., 27,
Doshomachi 2-chome, Higashi-ku Osaka, 541 (JP)

43 Date of publication of application: 01.06.83
Bulletin 83/22

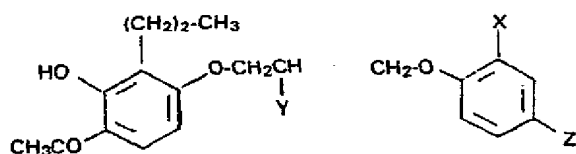
72 Inventor: Nohara, Akira, 15-12,
Oharano-Kamisatorimicho, Nishikyo-ku
Kyoto 610-11 (JP)
Inventor: Maki, Yoshitaka, 5-17,
Oharano-kamisatorimicho, Nishikyo-ku
Kyoto 610-11 (JP)

64 Designated Contracting States: BE CH DE FR GB IT LI
NL SE

74 Representative: Laredo, Jack Joseph et al, Elkington and
Fife High Holborn House 52/54 High Holborn, London,
WC1V 6SH (GB)

54 Diphenoxypropane derivatives, their production and use.

57 A diphenoxypropane derivative of the formula:



wherein X is a halogen atom, Y is a hydrogen atom or a hydroxy group and Z is a tetrazoyl or carboxy group, has an excellent antiasthmatic and antiinflammatory activities, and therefore the diphenoxypropane derivatives are useful as an antiasthmatic or antiinflammatory agent.

ACTORUM AG

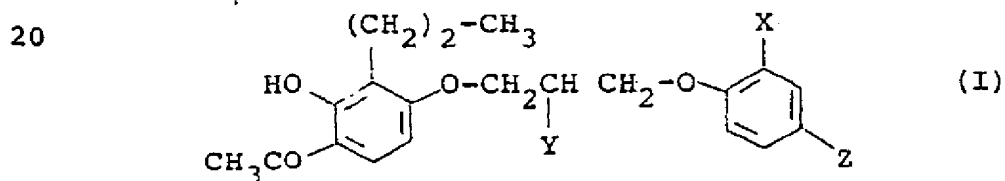
- 1 -

DIPHENOXYPROPANE DERIVATIVES, THEIR PRODUCTION AND USE

This invention relates to diphenoxypropane derivatives, a method of producing the same and their use.

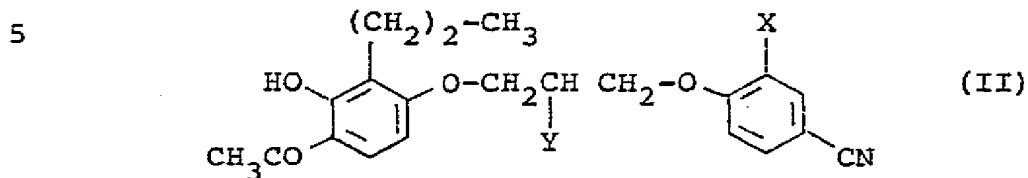
A synthetic search for the compounds which would antagonize chemical mediators exerting contractile effects on bronchial smooth muscle led to the discovery that certain diphenoxypropane derivatives are useful for the purpose. The diphenoxypropane derivatives according to this invention are subsumed in the general formula given in U.K. Patent Application Publication No. 2,058,785, but have not been specifically described in the working examples thereof. Under the circumstances the present inventors undertook a further pharmacological study of these diphenoxypropane derivatives and found that these diphenoxypropane derivatives have excellent activity. This finding was followed by further studies, on which this invention has been predicated.

Thus, the present invention relates to (1) a diphenoxypropane derivative (I) of the formula:

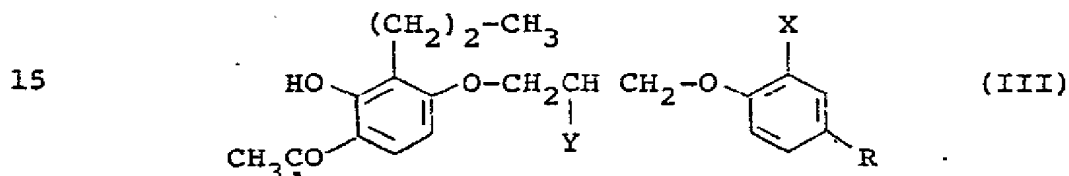


25 wherein X is a halogen atom, Y is a hydrogen atom or a hydroxy group, Z is a tetrazolyl or carboxy group;

(2) a method of producing a diphenoxypropane derivative (I), which comprises reacting a compound (II) of the formula:



10 wherein X and Y have the same meaning as defined above, with hydrazoic acid or a salt thereof or subjecting a compound (III) of the formula:



20 wherein X and Y are as defined above and R is a cyano, carbamoyl or alkoxycarbonyl group, to hydrolysis, and (3) an antiasthmatic or antiinflammatory agent which contains the diphenoxypropane derivative (I).

25 Referring to the above general formula, the halogen atom X may for example be chlorine, bromine, iodine or fluorine. Among them, chlorine and bromine are preferable.

In the present specification, the compound (I) wherein Z is a tetrazolyl group is sometimes referred to as "compound (I)-A", and the compound (I) wherein Z is a carboxy group is sometimes referred to as "compound (I)-B".

30 The compound (I)-A according to this invention is produced by the following procedure. Thus, it is produced by reacting a compound (II) with hydrazoic acid or a salt thereof. The salt of hydrazoic acid as used in this reaction is exemplified by salts of hydrazoic acid with alkali metals (e.g. lithium azide, sodium azide, potassium azide, etc.), salts of hydrazoic acid with alkaline earth metals

35

(e.g. magnesium azide, calcium azide, barium azide, strontium azide), salts of N_3H with other metals which are capable of forming salts therewith (e.g. aluminum azide, tin azide, titanium azide), salts of hydrazoic acid with ammonia or organic bases such as aniline, etc. While these salts of hydrazoic acid may be used independently, it is possible to use an alkali metal salt of hydrazoic acid, e.g. sodium azide, in combination with a Lewis acid (e.g. aluminum chloride, stannic chloride, zinc chloride, titanium tetrachloride) or ammonium chloride. It is likely that in such a combination, the alkali metal azide forms a hydrazoate with the cation of the compound used in combination, e.g. aluminum azide, tin azide, zinc azide, titanium azide, ammonium azide or the like, and this hydrazoate reacts with the starting compound (II). Among hydrazoic acid, salts thereof and combinations of salts, the combination of sodium azide with ammonium chloride is particularly desirable.

Generally, the reaction is desirably conducted in an organic solvent. Examples of such solvent include hydrocarbons such as benzene, toluene, petroleum ether, etc., ethers such as tetrahydrofuran, dioxane, ethylene glycol dimethyl ether, etc., acetonitrile, dimethylformamide, formamide, dimethyl sulfoxide, etc. The temperature, time and other conditions of the reaction are not particularly critical, but the reaction is generally conducted at about 50 to 150°C for about 1 hour to 2 days.

When a salt of hydrazoic acid is used as another reactant in this reaction, the compound (I)-A is produced in the form of a salt corresponding to the salt of hydrazoic acid used due to the acidity of the tetrazole ring and this salt can be easily converted to the desired compound (I)-A having a free tetrazole ring by treating it with a suitable acid (such as a mineral acid, e.g. hydrochloric acid, sulfuric acid, etc.).

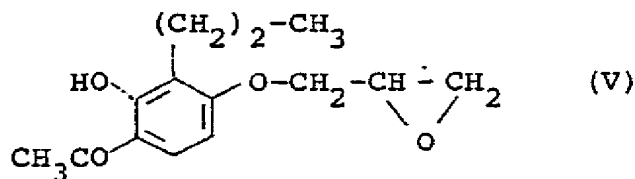
Moreover, an organic amine salt, amino acid salt,

alkali metal salt or ammonium salt, for instance, of the compound (I)-A can be produced by reacting (I)-A with an organic amine such as ethanolamine, dl-methylephedrine, 1-(3,5-dihydroxyphenyl)-L-isopropylaminoethanol, isoproterenol, dextromethorphan, hetrazan (diethylcarbamazine), etc., an amino acid such as L-lysine, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, etc., or ammonia in the per se conventional manner, e.g. mixing and heating in a suitable solvent.

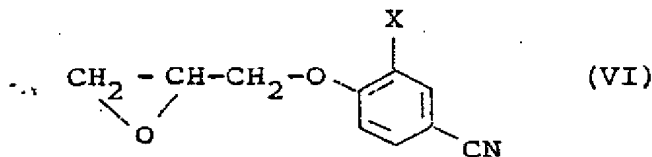
The starting compound (II) of this invention wherein Y is a hydroxy group can be produced by reacting a compound of the formula:



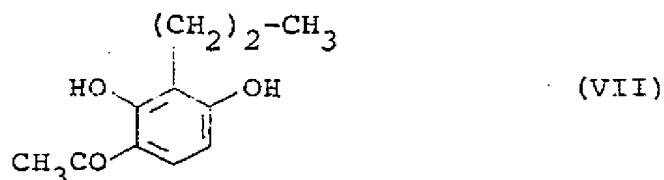
wherein X is defined as above, with a compound of the formula:



or by reacting a compound of the formula:



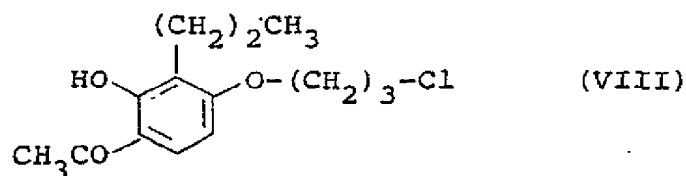
wherein X is defined as above, with a compound of the formula:



5

The starting compound (II) of this invention wherein Y is a hydrogen atom can be produced by reacting a compound of general formula (IV) with a compound of the formula:

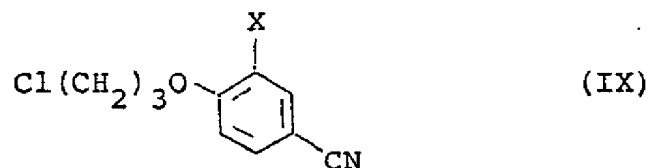
10



15

or by reacting a compound (VII) with a compound of the formula:

20



wherein X is defined as above.

25

The reaction is preferably conducted in the presence of a base. The base is exemplified by ammonium hydroxide (e.g. benzyltrimethylammonium hydroxide, benzyltriethylammonium hydroxide), organic amines (e.g. triethylamine, tributylamine), and alkali carbonate (e.g. anhydrous potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate).

30

Generally, the reaction is desirably conducted in an organic solvent. As examples of such organic solvents may be mentioned dimethylformamide, formamide, dimethyl sulfoxide, hexamethylphosphoric triamide, various ethers (e.g. tetrahydrofuran, dioxane), alkyl halides (e.g. chloroform, dichloromethane), etc. While the reaction temperature, time and other conditions are not especially

35

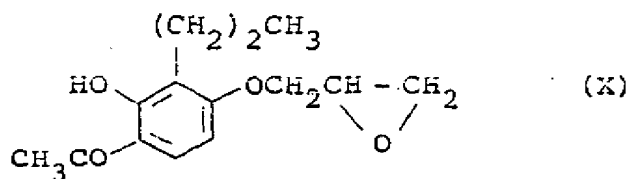
critical, the reaction is generally conducted at room temperature to about 180°C for about 1 to 24 hours.

The compound (I)-B can be produced by the following method. Thus, compound (I)-B are produced by subjecting the compound (III) to hydrolysis with an acid or alkali. The acid to be used in hydrolysis includes, among others, sulfuric acid, hydrochloric acid or other inorganic acids, and the alkali includes such hydroxides as sodium hydroxide, potassium hydroxide, lithium hydroxide or barium hydroxide. Generally, the reaction is preferably carried out in an organic solvent. The solvent includes, among others, alcohols such as methanol, ethanol or propanol, organic acids such as acetic acid or formic acid, and ethers such as tetrahydrofuran or dioxane. The reaction temperature, reaction time and other reaction conditions are not critical, but in general the reaction is carried out at a temperature between about 50°C and about the boiling point of the solvent used for about 1 to 48 hours.

Moreover, an organic amine salt, amino acid salt, alkali metal salt or ammonium salt, for instance, of the compound (I)-B can be produced by reacting the compound (I)-B with an organic amine such as ethanolamine, dl-methylephedrine, 1-(3,5-dihydroxyphenyl)-L-isopropyl-aminoethanol, isoproterenol, dextromethorphan, hetrazan (diethylcarbazine), etc., and amino acid such as L-lysine, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, etc., or ammonia in the per se conventional manner, e.g. mixing and heating in a suitable solvent.

The starting compound (III) in which Y is a hydroxy group, can be prepared, for example, by reacting a compound of the formula:

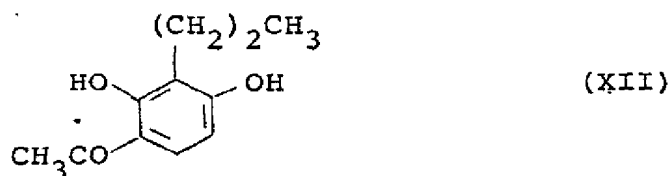
- 7 -



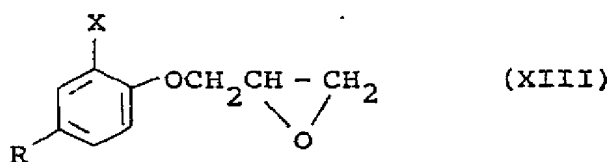
with a compound of the formula:



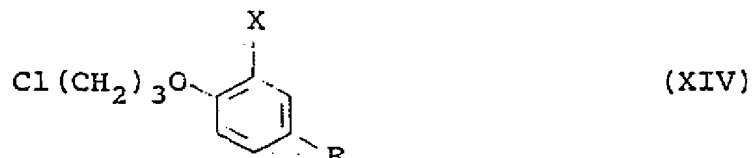
wherein X and R are as defined above, or by reacting a compound of the formula:



20 with a compound of the formula:



wherein X and R are as defined above. The compound (III) in which Y is a hydrogen atom can be prepared, for example, by reacting the compound of formula (XII) with a compound of the formula:



35 wherein X and R are as defined above.

The reaction is preferably conducted in the presence

of a base. The base is exemplified by ammonium hydroxide (e.g. benzyltrimethylammonium hydroxide, benzyltriethylammonium hydroxide), organic amines (e.g. triethylamine, tributylamine), and alkali carbonate (e.g. anhydrous potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate).

Generally, the reaction is desirably conducted in an organic solvent. As examples of such organic solvents may be mentioned dimethylformamide, formamide, dimethyl sulfoxide, hexamethylphosphoric triamide, various ethers (e.g. tetrahydrofuran, dioxane), alkyl halides (e.g. chloroform, dichloromethane), etc. While the reaction temperature, time and other conditions are not especially critical, the reaction is generally conducted at room temperature to about 180°C for about 1 to 24 hours.

In cases where R is a cyano group, said compounds may be converted either to the compound (I)-B by directly subjecting to hydrolysis or to the compound (III) in which R is an ester group by reacting with an alcohol such as methanol or ethanol in the presence of an acid such as sulfuric acid or hydrochloric acid.

The compound (I) according to this invention exhibits an antagonistic action on the slow reacting substance of anaphylaxis (SRS-A) which is a chemical mediator known to induce a contraction of bronchial and other smooth muscles.

Furthermore, compound (I) displays antiinflammatory activity as well.

SRS-A is produced by various stimuli such as immune reactions and has been considered to be an important mediator of bronchospasm in immediate allergies such as allergic asthma. There are several types of SRS-A, such as leukotriene C(LTC), leukotriene D(LTD), etc., and it is known that LTD and LTC are substantially equivalent in activity on the human bronchial muscle and that LTD is superior to LTC in constrictive effect on the guinea pig ileum [S.E. Dahlen et al., Nature 288, 484 (1980); R.A.

Lewis et al., Biochemical and Biophysical Research Communications 96, 271 (1980)]. The antagonistic effect of drugs against SRS-A can be investigated using the guinea pig ileum [R.A. Appleton et al., Journal of Medicinal Chemistry 20, 371 (1977)] and since SRS-A is a mixture of LTC, LTD, etc., it is desirable to use a synthetic SRS-A in the investigation of antagonistic activity.

The present inventors studied the antagonistic action of compound (I)-A against SRS-A using a synthetic LTD₄ in the following manner.

(1) Test method

The inhibitory effect of the drug on the contractile response (60-70% of maximum contraction) of the ileum of guinea pig (body weight 300-350 g, female and male) to leukotriene D₄ (LTD₄) was investigated. In Tyrode solution containing atropine (10⁻⁷ M) and mepyramine (10⁻⁶ M), 3 x 10⁻¹⁰ or 10⁻⁹ M of LTD₄ was repeatedly permitted to act on the guinea pig ileum and after the amplitude of contraction had become constant, a solution of the test drug was added to a final concentration of 10⁻⁹ to 10⁻⁴ M. After 1 minute, the same concentration of LTD₄ was further added and the anti-SRS-A activity of the drug was calculated from the change in contraction amplitude by means of the following equation.

$$\text{Percent inhibition} = \frac{\text{Amplitude of LTD}_4\text{-induced contraction before addition of drug} - \text{Amplitude of LTD}_4\text{-induced contraction after addition of drug}}{\text{Amplitude of LTD}_4\text{-induced contraction before addition of drug}} \times 100$$

To obtain the IC₅₀ value, the mole concentration of the drug showing a 50% inhibition of the contractile response was determined from plots on a graph.

The drug was used as dissolved in dimethyl sulfoxide. The solvent was used in an amount less than 1% which would not exert any influence on the ileum.

(2) Results

The concentrations of compounds necessary to cause a 50% inhibition of the LTD₄-induced contraction (60 to 70% of maximum contraction) of the guinea pig ileum are shown in IC₅₀ (M) values below.

Table 1 Anti-SRS-A activity

	Drug	IC ₅₀ (M)
	Compound (I)-A-1	4.1×10^{-9}
10	Compound (I)-A-2	1.9×10^{-8}
	Compound (I)-A-3	7.0×10^{-8}
	Control compound-1	4.2×10^{-7}
	Control compound-2	6.8×10^{-7}

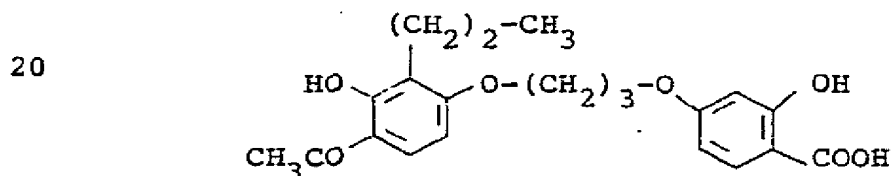
(Note)

15 Compound (I)-A-1 : Compound (I)-A wherein X=Cl and Y=OH

Compound (I)-A-2 : Compound (I)-A wherein X=Br and Y=OH

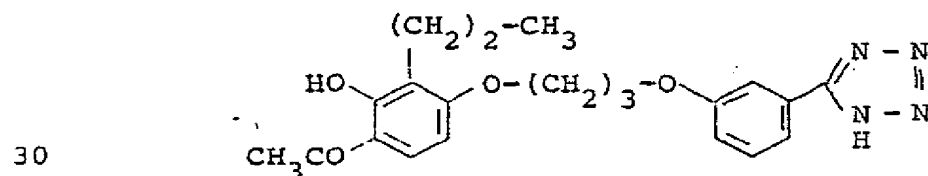
Compound (I)-A-3 : Compound (I)-A wherein X=Cl and Y=H

Control compound-1: Compound which has the formula:



[See U.K. Patent Application Publication No. 2,058,785, Example 8].

Control compound-2: Compound of the formula:



[See U.K. Patent Application Publication No. 2,058,785, Example 10 (b)]

The above test results indicate that the compound (I)-A according to this invention is superior to the compounds shown in the examples of U.K. Patent Application

Publication No. 2,058,785.

Furthermore, against the bronchoconstriction in guinea pigs due to an intravenous administration of synthetic leukotriene D₄ (LTD₄), compound (I)-A-1 as
5 intravenously administered 2 minutes before LTD₄ dosing displayed a remarkable inhibitory effect.

(1) Test method

Guinea pigs of Hartley strain, both male and female, with body weights about 400 g were assigned to groups of
10 6 individuals, and the bronchoconstriction due to LTD₄ were measured according to the method of Konzett-Rössler, [Konzett, H. and Rössler, R.: Naunyn-Schmiederbergs Archiv für Experimentelle Pathologie und Pharmakologie 195, 71-74 (1940)]. Each guinea pig was fixed in supine
15 position under urethane anesthesia (1.5 g/kg, intraperitoneal) and the trachea was incised and connected to an artificial respiration apparatus, Rodent Respirator Model 680 [Harvard Apparatus Company, U.S.A.] via a cannula. The branch tube of this tracheal cannula was connected to
20 Bronchospasm Transducer Model 7020 [Ugobasil Biological Research Apparatus, Italy]. Under the conditions of 5 to 7 ml of air per stroke, 70 strokes per minute and a lung loading pressure of 10 cmH₂O, the volume of overflowing air was recorded on Rectigraph-8S (Sanei Sokki Ltd.,
25 Japan) via a transducer. After administration of gallamine triethiodide (1 mg/kg, i.v.), 10 µg/kg of histamine·2HCl was intravenously administered to investigate the response of the animal. Then, a solution of LTD₄ in physiological saline (10 µg/kg) was intravenously administered and the
30 bronchoconstriction elicited thereby was recorded for 15 minutes. Two minutes before LTD₄ loading, compound (I)-A-1 was intravenously administered in a volume of 0.1 ml per 100 g body weight. Compound (I)-A-1 and LTD₄ were
35 administered through a cannula inserted into the jugular vein.

The compound (I)-A-1 was used as dissolved in

- 12 -

physiological saline containing sodium hydrogen carbonate, and LTD₄ was taken from a stock stored in methanol (1 mg/1 ml methanol) at -70°C.

(2) Result

5 Effect of compound (I)-A-1 against bronchoconstriction due to LTD₄:

The bronchoconstriction induced by intravenous administration of 10 µg/kg of LTD₄ as given 2 minutes after the administration of physiological saline was
10 maximal at the time of 30 seconds after the administration of LTD₄ and, since then, was rapidly attenuated to about 50% at the time of 2 minutes but lasted till 15 minutes. Assuming that the response at complete obstruction is 100%, the values at 30 seconds and 15 minutes were
15 47.4 ± 6.9% (n=6, Mean ± S.E.) and 19.4 ± 2.8% (Mean ± S.E.), respectively (S.E.: standard error).

The administration of Compound (I)-A-1 at the dose levels of 0.08, 0.313, 1.25 and 5 mg/kg at the time of 2 minutes before LTD₄ dosing inhibited the above response
20 by 39, 41, 51 and 93%, respectively, relative to the maximum response. Thus, at the intravenous dose of 5 mg/kg, a substantially complete inhibition could be accomplished (See Table 2, below). These results support the in vitro anti-SRS-A activity data.

25

Table 2

Compound	Dosage (mg/kg, i.v.)	Number of animals	Percent increase of overflow	Percent inhibition
Physiological saline	-	6	47.4 ± 6.9	-
30 Compound (I)-A-1	0.08	8	29.1 ± 7.5	39
Compound (I)-A-1	0.313	6	28.1 ± 7.1	41
Compound (I)-A-1	1.25	6	23.4 ± 8.0*	51
Compound (I)-A-1	5	6	3.3 ± 2.1***	93

35

Note: Significant difference in relation to physiological saline control:

*p<0.05, ***p<0.001, i.v. = intravenous administration

Furthermore, as will be apparent from the test result given below, the compound (I)-A-1 has an antiinflammatory activity.

Carrageenin oedema in rats:

5 The volume of the right hind paw of each rat was measured and the test compound suspended in 4% gum arabic solution was orally administered in an amount of 1 ml/100 g body weight. Immediately thereafter, a further amount of water was given to make the total dosing volume 5 ml.

10 After 1 hour, 0.05 ml of a 1% suspension of carrageenin in physiological saline was subcutaneously injected into the foot pad. Three hours after the carrageenin injection, the volume of the paw was measured again and the volume of the edema was calculated as a difference between this

15 measured volume of the paw and the volume before the injection.

 In the case of intravenous administration, a solution of the test compound in an aqueous solution of NaHCO_3 was intravenously administered in an amount of 2.0 ml/100 g

20 body weight and 5 ml of water per animal was orally administered. Then, carrageenin was injected subcutaneously to produce oedema.

Table 3

25	Test compound	Dosage (mg/kg)	Route of administration	Mean volume of oedematous swelling	Percent inhibition
				\pm S.E.	
	Control	-	p.o.	0.573 ± 0.021	-
	Compound (I)-A-1	50	p.o.	$0.487 \pm 0.023^*$	15.0
	Control	-	i.v.	0.547 ± 0.034	-
30	Compound (I)-A-1	1	i.v.	0.442 ± 0.044	19.2
	Compound (I)-A-1	10	i.v.	$0.410 \pm 0.046^*$	25.0

(Note) * : $p < 0.05$

p.o.: oral

35 i.v.: intravenous

S.E.: standard error

The acute toxicity of compound (I)-A-1 in mice was found to be as follows.

(1) Method

Five 5-week-old male mice of Jcl:ICR strain, weighing 26.0 to 30.5 g, were used. Compound (I)-A-1 was suspended in a 5% solution of gum arabic and administered orally by gastric gavage at the level of 0.2 ml per 10 grams body weight.

(2) Results

The oral administration of compound (I)-A-1 in a dose of 500 mg/kg caused no symptoms that could be attributable to compound (I)-A-1. Autopsy after 1 week did not reveal any abnormalities.

Then the present inventors studied the antagonistic action of the compound (I)-B against SRS-A using a synthetic LTD₄ in the manner described on the compound (I)-A.

(Note)

Compound (I)-B-1: Compound (I)-B wherein X=Cl and Y=OH
Compound (I)-B-2: Compound (I)-B wherein X=Cl and Y=H

The results are shown in Table 4.

In each case, the bronchoconstriction following intravenous administration of 10 µg/kg of LTD₄ at 2 or 30 minutes after the administration of physiological saline reached a maximum 30 seconds after the administration of LTD₄, and then decreased to about 50% at 2 minutes after the administration of LTD₄. The response continued for 15 minutes after the administration of LTD₄. Repeated experiments using 6 animals per group gave mean degrees of maximum bronchoconstriction (30-second values) of 52.2-67.1% and 54.7-70.1%, respectively, as compared with the state of complete obstruction (100%). In experiment 1, the test compounds (I)-B-1, (I)-B-2 and Control compound-1 were each intravenously administered at two minutes before the administration of LTD₄ and inhibitory effect

- 15 -

on the bronchoconstriction was examined. The minimum effective doses (causing statistically significant differences as compared with the control group; significance level <5%) were 0.313, 0.313 and 5 mg/kg, respectively. The corresponding inhibition percentages were 41, 52 and 56%, respectively. In experiment 2, the test compounds were intravenously administered 30 minutes before the administration of LTD₄ and the effect on the above response was examined. The minimum effective doses were 5, 5, and 20 mg/kg, respectively.

The above results thus proved that Compounds (I)-B-1 and (I)-B-2 are superior to Control compound-1 in the inhibitory effect upon the bronchoconstriction.

Table 4

Compound	% Inhibition			
	Dose (mg/kg, i.v.)			
	0.313	1.25	5	20
Experiment 1				
Compound (I)-B-1	41*	51**	84***	NT
Compound (I)-B-2	52*	77**	79**	NT
Control compound-1	NT	14	56***	87***
Experiment 2				
Compound (I)-B-1	NT	NT	42**	96***
Compound (I)-B-2	NT	10	42**	66***
Control compound-1	NT	NT	14	35**

Notes:

Experiment 1: The test compounds were intravenously administered 2 minutes before the intravenous administration of 10 µg/kg of LTD₄.

Experiment 2: The test compounds were intravenously administered 30 minutes before the intravenous administration of 10 µg/kg of LTD₄.

BAD ORIGINAL

% Inhibition: Each value was calculated from the volume (in percentage) of air overflowing from the respiratory tract at the time when the response was maximal, i.e. 30 seconds after the administration of LTD₄.

5 NT: Not tested.

*P<0.05, **P<0.01, ***P<0.001 (against the control group)

Further, studies were carried out on antigen-induced bronchoconstriction in sensitized guinea pigs using the compounds (I)-B-1, (I)-B-2 and the Control compound-1.

10 According to the method of Orange and Moore [Orange, R. P. and Moore, E. G., Journal of Immunology, 116, 392-397 (1976)], Hartley-strain male guinea pigs weighing about 350 g were sensitized by intraperitoneal administration of 1 ml of an emulsion composed of 0.5 ml of physiological
15 saline containing 1 mg of egg albumin (EA) and 0.5 ml of Freund's complete adjuvant (Difco, USA). Three weeks after the sensitization, the serum antibody levels in the sensitized guinea pigs were determined by the 3-hour PCA reaction in guinea pigs and those guinea pigs that gave
20 positive results in the PCA reaction with 1,000-fold diluted serum samples therefrom were used as the sensitized animals. Using the Konzett-Rössler method as mentioned under the above paragraph i), the bronchoconstriction due to the antigen-antibody reaction was induced by
25 intravenous administration of 1 mg/kg of the antigen EA instead of LTD₄, and recorded.

The results are shown in Table 5.

The bronchoconstriction in the control group as induced by antigen administration 2 minutes after the
30 intravenous administration of physiological saline reached a maximum one minute after the intravenous administration of the antigen. Gradual recovery followed and the pre-treatment state was almost restored in 15 minutes after the induction. Repeated experiments using 6 animals per
35 group gave mean degrees of maximum bronchoconstriction (one-minute values) of 72.8-83.3% as compared with the

state of complete obstruction (100%). The test compounds (I)-B-1, (I)-B-2 and Control compound-1 were each intravenously administered 2 minutes prior to antigen administration and the inhibitory effect on the bronchoconstriction was examined. The minimum effective doses were 5, 5 and 20 mg/kg, respectively, and the corresponding inhibition percentages were 51, 52 and 64%, respectively.

The above results indicated that Compounds (I)-B-1 and (I)-B-2 are superior to Control compound-1 in the inhibitory effect on the antigen-induced bronchoconstriction.

Table 5

Compound	% Inhibition		
	Dose (mg/kg, i.v.)		
	1.25	5	20
Compound (I)-B-1	6	51***	75***
Compound (I)-B-2	20	52**	88***
Control compound-1	12	16	64***

Notes:

The test compounds were intravenously administered 2 minutes prior to intravenous administration of the antigen.

% Inhibition: Each value was calculated from the volume (in percentage) of air overflowing from the respiratory tract at the time when the response was maximal, i.e. one minute after administration of the antigen.

p<0.01, *p<0.001 (against the control group).

The acute toxicity of compounds (I)-B-1 and (I)-B-2 in mice was found to be as follows.

(1) Method

Five 5-week-old male mice of Jcl:ICR strain, weighing 26.0 to 30.5 g, were used. Compound (I)-B-1 or (I)-B-2 was

suspended in a 5% solution of gum arabic and administered orally by gastric gavage at the level of 0.2 ml per 10 grams body weight.

(2) Result

5 The oral administration of compound (I)-B-1 or (I)-B-2 in a dose of 500 mg/kg caused no symptoms that could be attributable to compound (I)-B-1 or (I)-B-2. Autopsy after 7 days did not reveal any abnormalities.

10 It will thus be apparent that the compound (I) according to this invention is useful in the treatment of diseases due to SRS-A, such as asthma, hay fever, chronic bronchitis, allergic diseases of the eye, allergic diseases of the stomach and intestines, cardiovascular disturbances, allergic dermatitis and other inflammatory
15 diseases. For example, as an antiasthmatic or antiinflammatory drug, the compound (I) or said salt thereof can be administered orally or parenterally to mammalian animals (e.g. mouse, rat, guinea pig, man) in a daily dose of about 1 to 20 mg/kg.

20 For oral administration, the compound (I) or salt thereof can be formulated with a pharmaceutically acceptable carrier (e.g. lactose, starch, cellulose derivatives, stearic acid, magnesium stearate, sucrose, gelatin, gum arabic) and processed into such dosage forms
25 as tablets, capsules, granules, troches, liquid, syrup, etc. For parenteral administration, the compound (I) or salt thereof can be formulated with pharmacologically acceptable vehicles (e.g. vaseline, hydrophilic ointment bases; oleaginous bases, glyceride, polyethylene glycol,
30 etc.) and processed into ointments, suppositories, aerosols, inhalants, injections, etc. These dosage forms may be produced by the established pharmaceutical procedures.

The following Reference Examples and Examples illustrate the present invention in more detail.

35

Reference Example 1

To a solution of 4-cyano-2-chlorophenol (612 mg),

dimethylformamide (2 ml) and Triton B (Rohm and Haas, U.S.A.) (1 drop) was added 4-(2,3-epoxy)propyl-2-hydroxy-3-n-propylacetophenone (500 mg), and the mixture was heated at 170°C for 0.5 hour. A further amount (500 mg) of 4-cyano-2-chlorophenol was added, and the mixture was further heated at 170°C for one hour. After the solvent was distilled off, a small amount of ethanol was added to the oily residue and the mixture was cooled to crystallize. The crystals were collected by filtration and recrystallized from ethanol to give 760 mg of crystals of 4-[3-(2-chloro-4-cyanophenoxy)-2-hydroxypropoxy]-2-hydroxy-3-n-propylacetophenone. m.p. 143-145°C.

Elemental analysis: $C_{21}H_{22}ClNO_5$

Calcd.: C, 62.45; H, 5.49; N, 3.47

Found : C, 62.38; H, 5.60; N, 3.29

Nuclear magnetic resonance spectrum ($CDCl_3$) δ :

12.65(1H,s), 7.38-7.65(3H,m), 6.97(1H,dd,J=2 and 8Hz), 6.43(1H,d,J=9Hz), 4.32(5H, pseudo-s), ca. 2.6(2H), 2.55(3H,s), ca. 1.43(2H,m), 0.90(3H,t,J=7Hz).

Infrared absorption spectrum (KBr) cm^{-1} :

3440, 2240, 1630, 1610

Reference Example 2

A mixture of 4-(2,3-epoxy)propyl-2-hydroxy-3-propylacetophenone (1 g), 3-bromo-4-hydroxybenzonitrile (792 mg), dimethylformamide (2 ml) and Triton B (1 drop) was heated at 170°C for one hour. The solvent was distilled off and after addition of water, the residue was extracted twice, with ethyl acetate, and the extract was washed with water and dried over sodium sulfate. The solvent was then distilled off and the residue was chromatographed on a column of silica gel (50 g) and eluted with a solution of chloroform-acetone-formic acid (100:1:0.1). This product was recrystallized from methanol to give 825 mg of 4-[3-(2-bromo-4-cyanophenoxy)-2-hydroxypropoxy]-2-hydroxy-3-propylacetophenone as colorless plates. m.p. 143-145°C

Elemental analysis: $C_{21}H_{22}BrNO_5$

Calcd.: C, 56.26; H, 4.95; N, 3.12

Found : C, 56.51; H, 4.96; N, 3.18

Nuclear magnetic resonance spectrum ($CDCl_3$) δ : -

5 12.62(1H,s), 7.72(1H,d,J=2Hz), 7.53(1H,d,J=9Hz),
7.52(1H,dd,J=2 and 8Hz), 6.93(1H,d,J=8Hz), 6.44(1H,
d,J=9Hz), 4.30(5H,m), 2.63(2H,t,J=7Hz), 2.54(3H,s),
1.52(2H,m), 0.89(3H,t,J=7Hz).

Infrared absorption spectrum (KBr) cm^{-1} :

10 3440, 2230, 1625, 1500

Reference Example 3

A mixture of 3-(2-chloro-4-cyanophenoxy)propyl
chloride (1.61 g), 2,4-dihydroxy-3-n-propylacetophenone
(1.27 g), potassium carbonate (970 mg), potassium iodide
15 (600 mg) and dimethylformamide (3 ml) was stirred under
heating at 120°C for 5 hours. The reaction mixture was
diluted with 1 N-HCl and extracted with ethyl acetate.
The extract was washed with water and dried over sodium
sulfate, and the solvent was distilled off. The residue
20 was cooled and the crystals which formed were collected
by filtration and recrystallized twice from methanol to
give 1.40 g of 1-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-3-
(2-chloro-4-cyanophenoxy)propane as colorless crystals
melting at 96-97°C.

25 Infrared absorption spectrum (KBr) cm^{-1} : 2225, 1640-1610.

Nuclear magnetic resonance spectrum ($CDCl_3$) δ :

12.69(1H,s), 7.56(1H, pseudo-s), 7.52(1H,d,J=9Hz),
7.48(1H,dd,J=2 and 8Hz), 6.93(1H,d,J=8Hz), 6.43(1H,
d,J=9Hz), 4.28(4H,t,J=5.5Hz), 2.62(2H,t,J=7Hz),
30 2.58(3H,s), 2.42(2H), 1.42(2H,m), 0.88(3H,t,J=7Hz).

Elemental analysis: $C_{21}H_{22}ClNO_4$

Calcd.: C, 65.03; H, 5.72; N, 3.61

Found : C, 65.34; H, 5.75; N, 3.72

Reference Example 4

35 A mixture of 2-chloro-4-cyanophenol (2.15 g), 3-
bromo-1-chloropropane (2.3 g), dimethylformamide (3 ml)

and potassium carbonate (1.5 g) was heated at 100°C for one hour. After the inorganic salt was filtered off, the solvent was distilled off and the residue was dissolved in chloroform. The solution was chromatographed on a column of silica gel (80 g) and eluted with a solution of petroleum ether-ethyl acetate (10:1) to give 3.06 g of 3-(2-chloro-4-cyanophenoxy)propyl chloride as a colorless oil.

Nuclear magnetic resonance spectrum (CDCl_3) δ :

7.51 (1H, d, J=2Hz), 7.60 (1H, dd, J=2 and 8Hz), 6.97 (1H, d, J=8Hz), 4.24 (2H, t, J=5.5Hz), 3.79 (2H, t, J=6Hz), 2.37 (2H, m)

Reference Example 5

While a solution of 2-chloro-4-cyanophenol (50 g) and epichlorohydrin (60.3 g) in ethanol (55 ml) was refluxed, a solution of potassium hydroxide (21.9 g) in ethanol (90 ml) was added dropwise over a period of 40 minutes and the reaction mixture was further refluxed for 100 minutes. After the mixture was cooled, water (50 ml) was added thereto and neutralized with 1 N hydrochloric acid. After the solvent was distilled off, the residue was extracted with diethyl ether. The extract was dried (over magnesium sulfate) and the diethyl ether was distilled off. The residue was distilled under reduced pressure to give 27 g of 3-chloro-4-(2,3-epoxy)propylbenzonitrile as a colorless oil. After crystallization, the crystals are recrystallized from isopropyl ether-ethyl acetate to give colorless needles. m.p. 71.0-71.8°C

Elemental analysis: $\text{C}_{10}\text{H}_8\text{ClNO}_2$

Calcd.: C, 57.30; H, 3.85; N, 6.68

Found : C, 57.16; H, 3.88; N, 6.60

Reference Example 6

A mixture of 2-chloro-4-cyanophenol (2.15 g), 3-bromo-1-chloropropane (2.3 g), dimethylformamide (3 ml) and potassium carbonate (1.5 g) was heated at 100°C for one hour. The inorganic salt was then filtered off and

the solvent was distilled off. The residue was dissolved in chloroform, chromatographed on a column of silica gel (80 g), and eluted with a solution of petroleum ether-ethyl acetate (10:1) to give 3-(2-chloro-4-cyanophenoxy)propyl chloride as a colorless oil (3.06 g).

Reference Example 7

A mixture of 1-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-3-(2-chloro-4-cyanophenoxy)propane (1.86 g), ethanol (30 ml) and concentrated sulfuric acid (10 ml) was refluxed for 6 hours and then cooled to room temperature. The crystals were collected by filtration and dissolved in chloroform, the solution was washed with a saturated aqueous sodium hydrogen carbonate solution and then with dilute hydrochloric acid and dried (sodium sulfate). Then, the chloroform was distilled off, and the residue was recrystallized from ethanol. There was obtained ethyl 4-[3-(4-acetyl-3-hydroxy-2-n-propylphenoxy)propoxy]-3-chlorobenzoate as colorless needles (1.1 g). Melting point 101°-102°C.

Reference Example 8

A mixture of 2-bromo-4-cyanophenol (3.96 g), 3-bromopropyl chloride (3.46 g), dimethylformamide (20 ml) and anhydrous potassium carbonate (3 g) was heated at 100°C for 0.5 hour. The inorganic salt was filtered off, and the filtrate was concentrated. The residue was chromatographed on a column of silica gel (90 g), and eluted with a solution of n-hexane-chloroform-acetone (20:10:1) to give 3-(2-bromo-4-cyanophenoxy)propyl chloride as a colorless oil (4.15 g).

Reference Example 9

A mixture of 2,4-dihydroxy-3-n-propylacetophenone (2.83 g), 3-(2-bromo-4-cyanophenoxy)propyl chloride (4.0 g), anhydrous potassium carbonate (2.00 g), potassium iodide (200 mg) and dimethylformamide (10 ml) was heated at 120°C for 2 hours. The reaction mixture was then diluted with water, and extracted three times with ethyl

acetate. The extract was washed with water and dried over sodium sulfate, the ethyl acetate was distilled off, and the residue was recrystallized from methanol to give 1-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-3-(2-bromo-4-cyanophenoxy)propane as pale brown needles (3.96 g). Melting point 88-89°C.

Reference Example 10

A mixture of 1-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-3-(2-bromo-4-cyanophenoxy)propane (2.5 g), ethanol (35 ml) and concentrated sulfuric acid (10 ml) was refluxed for 6 hours and then allowed to stand at room temperature. The crystals were collected by filtration and dissolved in chloroform, and the solution was washed with aqueous sodium hydrogen carbonate and then with 1 N hydrochloric acid and dried over sodium sulfate. The solvent was distilled off and the residue was recrystallized from ethanol to give ethyl 4-[3-[(4-acetyl-3-hydroxy-2-n-propyl)phenoxy]propoxy]-3-bromobenzoate as colorless needles (1.70 g). Melting point 99-100°C.

Reference Example 11

A mixture of 2-bromo-4-cyanophenol (1.584 g), 4-(2,3-epoxypropyl)-2-hydroxy-3-n-propylacetophenone (2.0 g), dimethylformamide (3 ml) and Triton B (one drop) was heated at 160-170°C for one hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was dried over sodium sulfate, the solvent was distilled off, and the residue was crystallized by adding methanol. Crystals of 4-[3-(2-bromo-4-cyanophenoxy)-2-hydroxypropoxy]-2-hydroxy-3-n-propylacetophenone (1.8 g) were obtained. Melting point 141-142°C.

Reference Example 12

A mixture of 2,4-dihydroxy-3-n-propylacetophenone (1.38 g), 3-chloro-4-(2,3-epoxypropyl)benzonitrile (1.5 g), dimethylformamide (3 ml) and Triton B (one drop) was heated at 160-170°C for 4 hours, then diluted with water and extracted with ethyl acetate. The extract was dried

over sodium sulfate, the solvent was distilled off, and the residue was crystallized from ethanol to give 4-[3-(2-chloro-4-cyanophenoxy)-2-hydroxypropoxy]-2-hydroxy-3-n-propylacetophenone as crystals (1.3 g). Melting point
5 143-145°C.

Example 1

A mixture of 4-[3-(2-chloro-4-cyanophenoxy)-2-hydroxypropoxy]-2-hydroxy-3-propylacetophenone (760 mg), ammonium chloride (760 mg), sodium azide (760 mg) and
10 dimethylformamide (2.5 ml) was heated at 120°C for 1 hour. After the inorganic salt was filtered off, the dimethylformamide was distilled off. 1 N-HCl was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with water and dried over sodium
15 sulfate, and the solvent was distilled off. The residue was chromatographed on a column of silica gel (25 g) and eluted with a solution of chloroform-acetone-formic acid (5:1:0.1). The fractions containing the desired product were combined and the solvent distilled off. To the
20 residue was added a further amount of ethanol and chloroform and the mixture was re-distilled to obtain 640 mg of 4-[3-[4-(tetrazol-5-yl)-2-chlorophenoxy]-2-hydroxypropoxy]-2-hydroxy-3-propylacetophenone as a colorless amorphous solid.

25 Infrared absorption spectrum (KBr) cm^{-1} :

3400, 1630, 1500, 1270, 1120, 1065

Nuclear magnetic resonance spectrum (DMSO- d_6) δ :

13.03(1H,s), 8.18(1H, pseudo-s), 8.10(1H,dd,J=2 and
9Hz), 7.90(1H,d,J=9Hz), 7.50(1H,d,J=9Hz), 6.77(1H,
30 d,J=9Hz), 4.33(5H, pseudo-s), 2.60(3H,s), 1.47(2H,m),
0.83(3H,t,J=7Hz)

Elemental analysis: $\text{C}_{21}\text{H}_{23}\text{ClN}_4\text{O}_5$

Calcd.: C, 56.44; H, 5.19; N, 12.54

Found: C, 56.02; H, 5.08; N, 12.66

35 Example 2

A mixture of 4-[3-(2-bromo-4-cyanophenoxy)-2-

hydroxypropoxy]-2-hydroxy-3-propylacetophenone (695 mg), ammonium chloride (600 mg), sodium azide (300 mg) and dimethylformamide (3 ml) was heated at 120°C for 1.5 hours, after which the inorganic salt was filtered off.

5 The filtrate was concentrated and dilute hydrochloric acid was added to the concentrate. The mixture was extracted twice with ethyl acetate and the extract was washed with water and dried. The solvent was then distilled off and the residue was chromatographed on a column of
10 silica gel (15 g), and eluted with a solution of chloroform-acetone-formic acid (5:1:0.1). The eluate was concentrated, petroleum ether was added to the residue, and the mixture was concentrated to dryness. The procedure gave 620 mg
15 of 2-hydroxy-3-propyl-4-[2-hydroxy-3-[2-bromo-4-(tetrazol-5-yl)phenoxy]propoxy]acetophenone as a colorless amorphous solid.

Infrared absorption spectrum (KBr) cm^{-1} :

3370, 1620, 1270, 1120, 1055, 1020

Nuclear magnetic resonance spectrum (DMSO- d_6) δ :

20 12.72(1H,s), 8.18(1H,d,J=2Hz), 7.99(1H,dd,J=2 and 8Hz), 7.73(1H,d,J=9Hz), 7.33(1H,d,J=8Hz), 6.63(1H,d,J=9Hz), 4.26(5H,s), 2.55(3H,s), ca. 1.41(2H,m), 0.81(3H,t,J=7Hz)

Elemental analysis: $\text{C}_{21}\text{H}_{23}\text{BrN}_4\text{O}_5$

25 Calcd.: C, 51.33; H, 4.72; N, 11.40

Found : C, 50.98; H, 4.59; N, 11.50

Example 3

A mixture of 1-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-3-(2-chloro-4-cyanophenoxy)propane (776 mg),
30 ammonium chloride (700 mg), sodium azide (700 mg) and dimethylformamide (2 ml) was heated at 120°C for 1 hour. After the inorganic salt was filtered off, the filtrate was concentrated under reduced pressure. The residue was acidified with 1 N-HCl and the resultant precipitate was
35 recovered by filtration. Recrystallized from methanol gave 659 mg of 1-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-

3-[2-chloro-4-(tetrazol-5-yl)phenoxy]propane as white microcrystals. m.p. 214-216°C

Infrared absorption spectrum (KBr) cm^{-1} : 3100, 1620

Nuclear magnetic resonance spectrum (DMSO- d_6) δ :

5 12.84(1H,s), 8.09(1H, pseudo-s), 8.02(1H,dd,J=2 and 8Hz), 7.80(1H,d,J=9Hz), 7.41(1H,d,J=8Hz), 6.68(1H, d,J=9Hz), 4.36(4H,m), 2.57(3H,s), ca. 2.4(4H,m), 1.47(2H,m), 0.83(3H,t,J=7Hz)

Elemental analysis: $\text{C}_{21}\text{H}_{23}\text{ClN}_4\text{O}_4$

10 Calcd.: C, 58.54; H, 5.38; N, 13.00

Found : C, 58.48; H, 5.31; N, 13.28

Example 4

A mixture of 4-[3-(2-chloro-4-cyanophenoxy)-2-hydroxy-propoxy]-2-hydroxy-3-n-propylacetophenone (180 mg), ethanol (3 ml) and concentrated sulfuric acid (0.6 ml) was heated at 100°C for 5 hours. The ethanol was then distilled off, the residue was diluted with water and extracted twice with ethyl acetate. The extract was washed with water and dried over sodium sulfate, the solvent was distilled off, and the residue was chromatographed on a column of silica gel (15 g) and eluted with a solution of chloroform-acetone-formic acid (20:1:0.1) to give an ester. Ethanol (2 ml) and a saturated aqueous sodium hydrogen carbonate solution (1 ml) were added to the ester, and the mixture was refluxed for 16 hours. The solvent was distilled off, the residue was acidified with 1N hydrochloric acid, and the mixture was extracted twice with ethyl acetate. The extract was washed with water and dried over sodium sulfate, the solvent was distilled off, and the residue was chromatographed on a column of silica gel (15 g), and eluted with a solution of chloroform-acetone-formic acid (7:1:0.1). The solvent was distilled off from the eluate, petroleum ether was added to the residue, and the white solid was collected by filtration and recrystallized from acetonitrile to give 4-[3-(4-acetyl-3-hydroxy-2-n-propylphenoxy)-2-hydroxypropoxy]-3-chlorobenzoic acid as colorless needles

(58 mg). Melting point 100-103°C.

Example 5

5 A mixture of ethyl 4-[3-(4-acetyl-3-hydroxy-2-n-propylphenoxy)propoxy]-3-chlorobenzoate (1.0 g), ethanol (10 ml) and 1 N sodium hydroxide (10 ml) was refluxed for 0.5 hour, then concentrated, acidified with 1 N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and concentrated, and the crystals were collected by
10 filtration. There was obtained 4-[3-(4-acetyl-3-hydroxy-2-n-propylphenoxy)propoxy]-3-chlorobenzoic acid as needles (840 mg). Melting point 171-172°C.

Example 6

15 A mixture of ethyl 4-[3-(4-acetyl-3-hydroxy-2-n-propylphenoxy)propoxy]-3-bromobenzoate (1.50 g), ethanol (15 ml) and 1 N sodium hydroxide (10 ml) was refluxed for 0.5 hour, then concentrated, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water and dried over sodium sulfate,
20 the solvent was distilled off, and the residue was chromatographed on a column of silica gel (50 g), and eluted with a solution of chloroform-acetone-formic acid (9:1:0.1). Recrystallization from ethyl acetate gave
25 4-[3-(4-acetyl-3-hydroxy-2-n-propylphenoxy)propoxy]-3-bromobenzoic acid as colorless needles (1.06 g). Melting point 180-182°C.

Example 7

30 A mixture of 4-[3-(2-bromo-4-cyanophenoxy)-2-hydroxypropoxy]-2-hydroxy-3-n-propylacetophenone (1.4 g), ethanol (12 ml) and concentrated sulfuric acid (4 ml) was refluxed for 4 hours, and then concentrated. Ethyl acetate and an aqueous sodium hydrogen carbonate solution were added. The ethyl acetate layer was separated and dried over sodium sulfate. The solvent was distilled off, and the residue
35 was chromatographed on a column of silica gel, and eluted with dichloromethane. To thus obtained oil

10

15.

25

30

42

200 mg/capsule

The above components are encapsulated by the established pharmaceutical procedure.

Example 11

5 Tablets

	(1) Compound (I)-B-1	20 mg
	(2) Lactose	150 mg
	(3) Corn starch	35 mg
	(4) Microcrystalline cellulose	30 mg
10	(5) Magnesium stearate	<u>5 mg</u>
		240 mg/tablet

The above components are admixed and tableted by the established pharmaceutical procedure.

Example 12

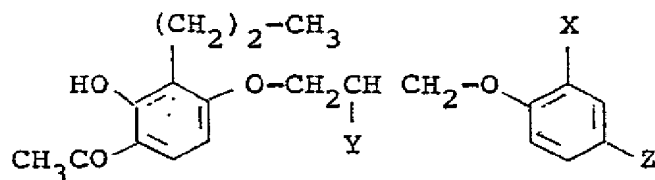
15 Capsules

	(1) Compound (I)-B-1	20 mg
	(2) Lactose	102 mg
	(3) Microcrystalline cellulose	70 mg
	(4) Magnesium stearate	<u>8 mg</u>
20		200 mg/capsule

The above components are encapsulated by the established pharmaceutical procedure.

What we claim is:

1. A compound of the formula:

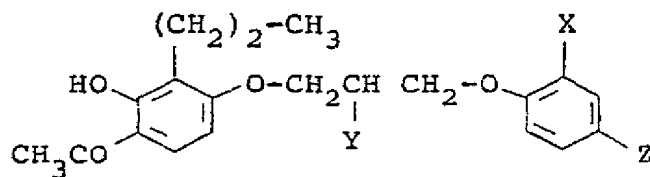


wherein X is a halogen atom, Y is a hydrogen atom or a hydroxy group and Z is a tetrazolyl or carboxy group.

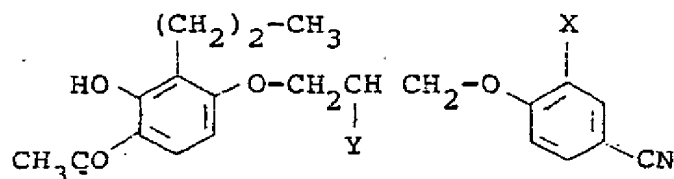
2. A compound as claimed in Claim 1, wherein Z is a tetrazolyl group.
3. A compound as claimed in Claim 1, wherein Z is a carboxy group.
4. A compound as claimed in Claim 1, wherein X is chlorine, Y is hydroxy and Z is tetrazolyl.
5. A compound as claimed in Claim 1, wherein X is chlorine, Y is hydrogen and Z is tetrazolyl.
6. A compound as claimed in Claim 1, wherein X is bromine, Y is hydroxy and Z is tetrazolyl.
7. A compound as claimed in Claim 1, wherein X is chlorine, Y is hydroxy and Z is carboxy.
8. A compound as claimed in Claim 1, wherein X is chlorine, Y is hydrogen and Z is carboxy.
9. A compound as claimed in Claim 1, wherein X is bromine, Y is hydroxy and Z is carboxy.
10. A compound as claimed in Claim 1, wherein X is

bromine, Y is hydrogen and Z is carboxy.

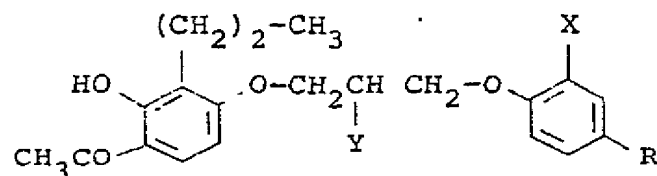
11. A method of producing a compound of the formula:



wherein X is a halogen atom, Y is a hydrogen atom or a hydroxy group and Z is a tetrazolyl or carboxy group, which comprises reacting a compound of the general formula:

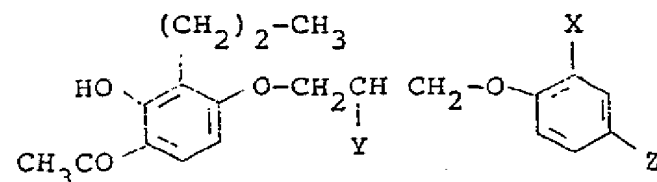


[X and Y are as defined above] with hydrazoic acid or a salt thereof, or subjecting a compound of the formula:



wherein X and Y are as defined above and R is a cyano, carbamoyl or alkoxycarbonyl group, to hydrolysis.

12. An antiasthmatic or antiinflammatory agent which contains a compound of the formula:



wherein X is a halogen atom, Y is a hydrogen atom or a hydroxy group and Z is a tetrazolyl or carboxy group.



European Patent
Office

EUROPEAN SEARCH REPORT

0080371

Application number

EP 82 30 6235

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 2)
D,X	<p>--- EP-A-0 028 063 (GLAXO GROUP) *Claims 1,9,10; page 30, lines 33-36*</p>	1-12	<p>C 07 C 65/40 C 07 D 257/04</p>
Y	<p>--- GB-A-1 516 747 (KLINGE PHARMA) *Page 23; claim 22*</p>	1,11	
Y	<p>--- GB-A-1 405 254 (MILES LABOR.) *Claim 1; page 4, example 12*</p>	1	
E,Y	<p>--- EP-A-0 056 172 (FISONS) *Claims 1,8,9,10; pages 20-21; example 4; page 26, line 21 - page 27, line 7*</p>	1,12	
A	<p>--- GB-A-1 533 820 (KLINGE PHARMA) *Claims 1,10*</p> <p>-----</p>	1,12	<p>TECHNICAL FIELDS SEARCHED (Int. Cl. 2)</p> <p>C 07 C 65/00 C 07 C 69/00 C 07 D 257/00</p>
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 28-02-1983	Examiner KLAG M.J.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO Form 1503 03/82